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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/038,080	01/03/2002	Peter C. Isakson	2891/3 (PHA 4142.2)	7358

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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 09/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/038,080	ISAKSON ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-16 and 19-27* is/are pending in the application.

4a) Of the above claim(s) *5,8,10 and 12-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4,6,7,9,11,15,16 and 19-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/27/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. The Response filed May 23, 2005 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.

Status of the Claims

3. Claims 1-18 were pending. Applicants added claims 19-27 and canceled claims 1, 17 and 18. Therefore, claims 2-16 and 19-27 are currently pending.

4. Claims 5, 8, 10 and 12-14 are drawn to non-elected species and/or inventions and thus these claims remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), there being no allowable generic claim.

5. Therefore, claims 2-4, 6, 7, 9, 11, 15, 16 and 19-27 are examined on the merits in this action.

Withdrawn Objections/Rejections

6. The Double Patenting rejections are withdrawn in view of Applicants' submission of two terminal disclaimers. All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claim Rejections - 35 USC § 112, first paragraph

7. Claims 2, 6, 7, 9 and 19-27 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 USC 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a written description rejection.

Applicants' claims are drawn to a composition comprising a broad genus of "selective" leukotriene B_4 receptor (LTB_4) antagonists that includes an unknown number (potentially infinite) of compounds (i.e., claims 2, 6, 7, 9 and 19-27).

In contrast, Applicants' specification only discloses a very limited number of potential "selective" LTB_4 receptor antagonists (e.g., see specification, pages 8 and 9 wherein "allegedly" 40 examples of small molecule selective LTB_4 receptor antagonists are disclosed; see also 35 U.S.C. 112, second paragraph rejections below).

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the claimed invention (e.g., see *In re Edwards*, 568 F.2d 1349, 1351-52, 196 USPQ 465, 467 (CCPA 1978); see also *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111 (CAFC 1991)). The "written description" requirement may be satisfied by using "such descriptive means as words,

structures, figures, diagrams formulas, etc., that fully set forth the claimed invention" (e.g., see *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966).

However, the Court also held that adequate written description requires more than a mere statement that a compound is part of the invention and reference to a potential method for isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. For example, the CAFC held that "trial and error" methods for isolating a compound do not provide adequate written support for such compounds if they have not yet been isolated (e.g., see *University of Rochester v. G.D. Searle & Co., Inc.* 69 USPQ2d 1886, 1889 (CAFC 2004)) (holding claims drawn to a method for inhibiting PGHS-2 enzymatic activity invalid for failure to meet the written description requirement because the patent "... neither disclose[d] any such compound nor provide[d] any suggestion as to how such a compound could be made or otherwise obtained other than by trial-and-error research"). Here, all of Applicants' claimed compounds that are not structurally related to the examples disclosed in the specification could only be obtained via "trial and error" research. Thus, the full breadth of Applicants' claimed scope fails the *Rochester* test.

Furthermore, Applicants provide no correlation between structure and function and/or any other identifying characteristics that would allow them to extend the teachings in their specification to the full scope of the current claims consistent with the PTO's guidelines (e.g., see *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 285 F.3d 1013 (Fed. Cir. 2002) wherein the court adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description"

Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics *when coupled with a known or disclosed correlation between function and structure* ... ." *Enzo*, 296 F.3d at 1324-25 (quoting Guidelines, 66 Fed. Reg. at 1106 (emphasis added)). For example, Applicants state, "With respect to MK-886 [and presumably MK-591 using similar logic, see 35 U.S.C. 112, second paragraph rejection below] ... one of skill in the art could not determine with confidence whether MK-866 [and MK-591] is a selective LTB_4 receptor antagonist as required by the instant specification [i.e., no structure/function relationship or identifying features]"; see also Noonan et al. reference cited therein). Consequently, Applicants' claimed scope represents only an invitation to experiment regarding other possible LTB_4 antagonists.

It is well settled that claiming only a result (i.e., the ability to selectively inhibit Cox-2 and/or LTB_4 inhibitors/antagonists) fails to satisfy the constitutional requisite of promoting the progress of science and the useful arts since this seeks to monopolize all possible ways to achieve a given result, far beyond those means actually discovered or contemplated by the inventor, so that others would have no incentive thereafter to explore a field already fully dominated. *O'Reilly v. Morse*, 15 How. 62, *In re Fuetterer*, 50 CCPA 1453, 1963 C.D. 620, 795 O.G. 783, 319 F.2d 259, 138 USPQ 217 ; *Siegel v. Watson*, 105 U.S. Appl. D.C. 344, 1959 C.D. 107, 742 O.G 863, 267 F.2d 621, 121 USPQ 119. Here, Applicants claims extend "far beyond" the means actually discovered and/or contemplated (i.e., a handful of alleged examples) and thus fail to satisfy the constitution requisite of promoting the progress of science and the useful arts.

Response

8. Applicant's arguments directed to the above written description rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive (except for claim 8, see below) for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "With respect to claims 2 and 9 ... Applicants establish possession of the invention because the specification provides a) identifying structure for more than 40 LTB_4 receptor antagonists within the scope of the claim, and b) the verbatim 'structural chemical formula' for the COX-2 inhibitor of the claim. Thus, claims 2 and 9 satisfy the written description requirement" (e.g., see 1/27/05 Response, pages 28-29).

[2] Applicants argue, "... there is no requirement, statutory or otherwise, to describe the common attributes or characteristics that identify all or a substantial portion of a genus ... Therefore, in view of the structural formula provided for COX-2 selective inhibitors [and also for the LTB_4 antagonists] ... the pending claims satisfy the written description requirement" (e.g., see 1/27/05 Response, pages 30-31). Applicants also note that the claims should not be interpreted in light of a vacuum and cite MPEP § 2173.02 in support of this position.

[3] Applicants argue, "With respect to claims 11, 15 and 16, Applicants respectfully request clarification of the rejection for lack of written description" (e.g., see 1/27/05 response, pages 31-32).

This is not found persuasive for the following reasons:

[1] The Examiner respectfully disagrees. The CAFC held that "trial and error" experimentation does not provide adequate written support for compounds that have yet to be discovered (e.g., see *University of Rochester v. G.D. Searle & Co., Inc.* 69 USPQ2d 1886, 1889 (CAFC 2004)) (a method for selectively inhibiting PGHS-2 enzymatic activity failed to meet the written description requirement because the patent "neither disclose[d] any such compound nor provide[d] any suggestion as to how such a compound could be made or otherwise obtained other than by trial-and-error research"). Here, all of the compounds that are not structurally related to the examples disclosed in Applicants' specification could only be obtained via "trial and error" research. Thus, Applicants' claimed scope encompasses compounds that fail the *Rochester* test. It is well settled that claiming only a result (i.e., the ability to selectively inhibit Cox-2 and/or LTB_4 inhibitors/antagonists) fails to satisfy the constitutional requisite of promoting the progress of science and the useful arts since this seeks to monopolize all possible ways to achieve a given result, far beyond those means actually discovered or contemplated by the inventor, so that others would have no incentive thereafter to explore a field already fully dominated. *O'Reilly v. Morse,* 15 How. 62, *In re Fuetterer*, 50 CCPA 1453, 1963 C.D. 620, 795 O.G. 783, 319 F.2d 259, 138 USPQ 217; *Siegel v. Watson*, 105 U.S. Appl. D.C. 344, 1959 C.D. 107, 742 O.G 863, 267 F.2d 621, 121 USPQ 119. Here, Applicants claims extend "far beyond" the means actually discovered and/or contemplated (i.e., the handful of examples disclosed in the specification) and thus fail to satisfy the constitution requisite of promoting the progress of science and the useful arts. Furthermore, Applicants claimed scope encompasses compound (e.g., MK-866, MK-599) that Applicants don't regard as their invention (e.g., see 35 U.S.C. 112, second paragraph rejections below, which are incorporated in their entirety herein by reference).

[2] The examiner has never stated that there is only one way to show possession of a claimed invention (e.g., see newly amended rejection above, "The 'written description' requirement may be satisfied by using 'such descriptive means as words, structures, figures, diagrams formulas, etc."). Furthermore, whether the COX-2 selective inhibitors or the selective LTB_4 receptor antagonists that are explicitly disclosed via molecular formula in Applicants' specification and claims has never been a contested issue. Consequently, Applicants' arguments are moot. The only issue here is whether the full breadth of Applicants' claims, which encompasses compounds that are NOT represented by molecular formula and could not be obtained by any other means than "trial and error" research, is adequately described. The Examiner contends that it is not for the reasons descried in the newly amended rejection above.

[3] Claims 11, 15 and 16 were not rejected.

Accordingly, the written description rejection cited above is hereby maintained.

Claims Rejections - 35 U.S.C. 112, second paragraph

9. Claims 2-4, 6, 7, 9, 11, 15, 16 and 19-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. 2-4, 6, 7, 9, 11, 15, 16 and 19-27

A. Claims 2-4, 6, 7, 9, 11, 15, 16 and 19-27 are rejected because the compounds in these claims are not defined with any chemical or physical characteristic, but only by functional properties (i.e., they act as a "selective leukotriene B_4 receptor antagonist" or "cyclooxygenase-2 selective inhibitor"). A claim to a material defined solely in terms of what it can do, or a property thereof, does not particularly point out the claimed

invention. A person of skill in the art cannot immediately envision all the possible chemical structures for a compound with this function. See *ex parte Pulvari* (POBA 1966) 157 USPQ 169.

Furthermore, Applicants have listed many "misleading" examples of "preferred" selective LTB_4 receptor antagonists in their specification that further exacerbates the problem. For example, the specification was recently amended to delete MK-886 from the list of "preferred" selective LTB_4 receptor antagonists (e.g., see 1/27/05 amendment; see also 1/27/05 Response, page 34, paragraph 2, "... this amendment ... remove[s] MK-886 from the listing of preferred LTB_4 receptor antagonists"). However, this amendment did not completely rectify the problem. For example, it is not clear why MK-591 was not likewise removed? MK-591 was specifically developed from MK-886 and, as such, is a structural and functional analog (e.g., see Pansit et al., Summary; see also page 243 for comparison of structures and biological activities). Thus, the line between what is [e.g., MK-591] and what is not [e.g., MK-886] a selective LTB_4 antagonist is simply not clear.

B. Claim 2-4, 6, 7, 9, 11, 15, 16 and 19-27 recite the term "selective." The term "selective" is a relative term, which renders the claim indefinite and/or unclear. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. See also MPEP § 2173.05(b). For example, the description listed on pages 7-9 of the specification only provides for "preferable" examples of selective Cox-2/ LTB_4 inhibitors/antagonists and, as such, does not rise to the level of an adequate definition for either term (i.e., the IC_{50} values, selectivity ratios, etc. referred to

by Applicants represent only "preferred" embodiments and thus cannot be used to define the term because these values are not "required").

Response

10. Applicant's arguments directed to the above 35 U.S.C. 112, second paragraph rejections were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or newly amended arguments.

[1] Applicants argue that they have adequately defined the term "selective leukotriene B_4 antagonist" in the specification and further provided "over 40 examples" of specific compounds that qualify as selective leukotriene B_4 receptor antagonists and cite various passages in the specification in support of this position (e.g., see 1/27/05 Response, pages 32-33).

[2] Applicants argue, "With respect to MK-886 ... one of ordinary skill in the art could not determine with confidence whether MK-886 is a selective LTB_4 receptor antagonist as required by the instant specification ... this amendment ... [therefore removes] MK-866 from the listing of preferred LTB_4 receptor antagonists" (e.g., see 1/27/05 Response, page 34).

[3] Applicants argue that they are "only" claiming selective compounds and, as a result, provide proper guidance for the term (e.g., see 1/27/05 Response, page 35).

This is not found persuasive for the following reasons:

[1] The Examiner respectfully disagrees. Applicants have not provided, for example, an adequate definition for the term "selective" LTB_4 antagonist and the "over 40 examples" are

misleading. For example, Applicants' specification does not even define the term "selective" LTB_4 antagonist and, as a result, Applicants' arguments are moot (the same rationale applies to the Cox-2 inhibitors). The passages cited by Applicants notably fail to draw the reader's attention toward the most important part of the definition, namely, the subject matter of what is being defined (e.g., page 8, lines 4-5, "The term 'leukotriene B_4 receptor antagonist' [i.e., the passage defines LTB_4 antagonist, NOT the currently claimed "selective" LTB_4 antagonist] embraces [i.e., comprises, see Webster's II New Riverside University Dictionary, page 427, wherein the dictionary defines "embrace" as "... **3.** To include, comprise, or contain"] compounds which selectively antagonize a leukotriene B_4 receptor"). Here, Applicants are not defining what a "selective" LTB_4 receptor antagonist is but, rather, what an LTB_4 receptor antagonist is in general (i.e., whether it is selective or not). In addition, the selectivity ratios and/or IC_{50} values referred to by Applicants represent only "preferred" embodiments and, as a result, do not constitute a definition for the term (e.g., see page 12/17/03 Response, page 36, "Preferably, the compounds have a cycloxygenase-2 IC_{50} of less than about 0.5 μM ..."). Thus, the functional language is indefinite because nothing in Applicants' specification provides a definition, structural correlation and/or any other means of curing the defects for Applicants' claimed functional language (see 35 U.S.C. 112, second paragraph rejection above).

Furthermore, the examples cited by Applicants in specification are misleading. The specification discloses compounds like "MK-591" as "preferred" LTB_4 antagonists (e.g., see specification, paragraph bridging pages 8-9, "Preferred leukotriene B_4 receptor antagonists include ... MK-591") (emphasis added). However, this is appears to be in error as MK-591 is structurally and functionally related to MK-866 (e.g., see newly amended rejection above),

which has been deleted from the "definition" and claims. Thus, Applicants specification and claims only serve to further confuse the definition of a "selective" LTB_4 receptor antagonist by treating very similar compounds (e.g., MK-591 and MK-886) differently with respect to their classification (i.e., whether or not they constitute a selective LTB_4 receptor antagonist).

[2] Although this is a step in the right direction, the Examiner contends that Applicants' 1/27/05 amendment does not go far enough to rectify the problem. First, it is not clear whether or not Applicants' deletion of MK-886 from the "preferred" list of compounds precludes MK-886 from the scope of Applicants' broad claims or, alternatively, just removes MK-886 from the scope of Applicants' more narrowly defined "preferred" embodiments. Second, Applicants' 1/27/05 amendment does not remove "equivalent" compounds that are closely related in structure and function (e.g., MK-591). For example, a person of skill in the art could not determine with confidence whether MK-591 is a selective LTB_4 receptor antagonist as required by the instant specification for the very same reason that Applicant provides for MK-886 (e.g., see 1/27/05 Response, page 34, paragraph 2 and Noonan et al. reference cited therein).

[3] The Examiner respectfully disagrees. All of the "guidance" provided by Applicants simply represents a "preferred" embodiment. Thus, Applicants are not bound to any particular IC_{50}, selectivity ratio, etc. and, as a result, a person of skill in the art could not determine what the metes and bounds of the claimed invention is.

Accordingly, the 35 U.S.C. 112, second paragraph rejection cited above is hereby maintained.

Claim Rejections - 35 USC § 103

11. Claims 2, 6, 7, 9 and 19-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ducharme et al. (US Pat. No. 5,474,995) (Filing Date is **January 10, 1994**; Date of Patent is **December 12, 1995**) (IDS Reference Number 60) and Rainsford, K. D. (Rainsford, K. D. "Leukotrienes in the pathogenesis of NSAID-induced gastric and intestinal mucosal damage" *Agents and Actions* **1993**, 39 (Spec. Conf. Issue), C24-C26) (of record).

For ***claims 2, 6, 7 and 9***, Ducharme et al. teach cycloxgenase-2 inhibitors and pharmaceutical compositions thereof with compounds of Formula I (e.g., see Ducharme et al. i.e., "1 of 2", Summary of Invention; see also Ducharme et al. "2 of 2", showing various compounds that fall within the scope of Formula I). For example, Ducharme et al. teach a Cox-2 inhibitor 3-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-furan (see column 6, entry "k", RN 157671-80-2) with the same formula as that claimed by applicants in Formula I of claim 2 wherein R^2 is an methyl, A is a furan ring (i.e., furyl), R^1 is a phenyl substituted with a fluoro, and R^3 is a hydrido (Please note that other examples also exist as shown throughout Ducharme et al.). Ducharme et al. also teaches that the above compounds of formula I "will be useful as a partial or complete substitute for conventional NSAID's in preparations wherein they are presently co-administered with other agents or ingredients" (see Ducharme et al., column 7, lines 65-67, "... compounds of formula I, will be useful as a partial or complete substitute for conventional NSAID's").

The prior art teachings of Ducharme et al. differ from the claimed invention as follows:

For ***claim 2, 6, 7 and 9***, although Ducharme et al. state that the Cox-2 inhibitors of formula I "... will be useful as a partial or complete substitute for conventional NSAID's in preparations wherein they are presently co-administered with other agents or ingredients" (see Ducharme et al., column 7, lines 65-67), they do not explicitly state that NSAID's are presently co-administered with a leukotriene B_4 antagonist.

For ***claims 19-27***, Ducharme et al. fail to recite Applicants claimed dosages for the combination of drugs.

However, Rainsford teaches the following limitations that are deficient in Ducharme et al.:

For ***claims 2, 6, 7 and 9***, Rainsford teaches that the leukotriene B_4 receptor antagonist, MK-886, can be beneficially co-administered with NSAIDs (e.g., see Rainsford, abstract) ("Gastric and intestinal mucosal lesions by NSAIDs were prevented by both prior (2-5 h) + 0.25 or 0 h oral dosing of the 5-lipoxygenase inhibitor, MK-886"). Hence, the combined teachings of Ducharme et al. and Rainsford teach a "combination" of Cox-2 inhibitors of formula I and leukotriene B_4 receptor antagonists like MK-886 (i.e., when the Cox-2 inhibitors disclosed by Ducharme et al. are "substituted" for the NSAIDs disclosed by Rainsford).

For ***claims 19-27***, Rainsford teaches the use of 10mg/kg, which is >> 0.5 mg/kg, for Indomethacin (i.e., the NSAID that is substituted by the compound of formula I as taught by Ducharme et al.) for a 12-15 kg rat that would teach approximately a 120-150 mg dosage (i.e., 10 mg/kg × 12-15 kg, see Rainsford, page C24, column 2, first full paragraph) of the selective cyclooxygenase-2 inhibitor of formula I (after substitution).

Rainsford also teaches the application of 30 mg/kg MK-886, which is >> 0.5 mg/kg, for a 12-15 kg rat that would teach approximately 360-450 mg dosage of the MK-886 compound selective leukotriene B4 receptor antagonist (e.g., see Rainsford, C25, column 1, last paragraph).

It would have been obvious to one skilled in the art at the time the invention was made to "substitute" the compounds of formula I as taught by Ducharme et al. for the NSAIDs in the preparations containing both NSAIDs and leukotriene B_4 antagonists (i.e., MK-886) as taught by Rainsford because Ducharme et al. explicitly state, "... compounds of formula I, will be useful as a partial or complete substitute for conventional NSAID's in preparations wherein they are presently co-administered with other agents or ingredients" (e.g., see Ducharme et al., column 7, lines 65-67). Furthermore, one of ordinary skill in the art would have been motivated to substitute the Cox-2 inhibitors as disclosed by Ducharme et al. for the NSAIDs as disclosed by Rainsford to lower the gastric mucosal lesions that normally associated with the NSAIDs (e.g., see Ducharme et al., column 7, lines 50-65, "By virtue of its high cycloxygenase-2 (Cox-2) activity and/or its selectivity for cyclooxygenase-2 ... compounds of formula I will prove useful as an alternative to conventional non-steroidal anti-inflammatory drugs (NSAID'S) particularly where such non-steroidal anti-inflammatory drugs may be contra-indicated such as in patients with peptic ulcers [e.g., gastric and intestinal mucosal lesions]"). Finally, a person of skill in the art would reasonably have been expected to be successful because Ducharme et al. explicitly state that such a substitution can be made and provide specific working examples (e.g., see Ducharme et al., column 7, lines 65-67; see also Examples).

Response

12. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "... as stated under the indefiniteness rejection section, the Applicants have amended the specification to delete MK-866 from the list of preferred LTB_4 receptor agonist ... Rainsford referred to MK-866 as a 5-lipoxygenase inhibitor and not a selective LTB_4 receptor agonist [and thus MK-866 presumably does not qualify as an LTB_4 receptor agonist]" (e.g., see 1/27/05 Response, page 40, second to last paragraph).

[2] Applicants argue, "Rainsford et al. stated in the discussion '[I]t appears essential to dose the 5-LO inhibitor, MK-886, for 3-5h, and 0.25-0h to reduce GI mucosal lesions.' In addition, on page C25 Rainsford states that '[N]o effects occurred when MK-886 was given as a single dose either at 0h or 3, 4, or 5h earlier with these NSAIDs (no data).' Therefore, one skilled in the art would not have been motivated to combined a COX-2 selective inhibitor with MK-886, let alone a selective LTB_4 receptor antagonist" (e.g., see 1/27/05 Response, page 40, last paragraph).

[3] Applicants argue, "... there would have been no reasonable expectation that the combination of a selective COX-2 inhibitor and a selective LTB_4 receptor antagonist would be successful based on the teachings of Ducharme and Rainsford" (e.g., see 1/27/05 Response, page 40, last paragraph).

This is not found persuasive for the following reasons:

[1] The Examiner contends that Applicants have not provided a clear definition for a "selective LTB_4 antagonist" (e.g., see newly amended 35 U.S.C. 112, second paragraph rejections above, which are incorporated in their entirety herein by reference) and, as a result, Applicants' arguments are moot.

[2] In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one of ordinary skill in the art would have been motivated to substitute the Cox-2 inhibitors as disclosed by Ducharme et al. for the NSAIDs as disclosed by Rainsford to lower the gastric mucosal lesions that normally associated with the NSAIDs (e.g., see Ducharme et al., column 7, lines 50-65, "By virtue of its high cycloxygenase-2 (Cox-2) activity and/or its selectivity for cyclooxygenase-2 ... compounds of formula I will prove useful as an alternative to conventional non-steroidal anti-inflammatory drugs (NSAID'S) particularly where such non-steroidal anti-inflammatory drugs may be contra-indicated such as in patients with peptic ulcers [e.g., gastric and intestinal mucosal lesions]"). Applicants cited passages (e.g., in the discussion and passages on page C25) only reinforce this "need" to make such a substitution (i.e., to further prevent the mucosal lesions that are noted to occur with the NSAIDs disclosed by Rainsford).

[3] The Examiner respectfully disagrees. A person of skill in the art would reasonably have been expected to be successful because Ducharme et al. explicitly state that such a substitution can be made and provide specific working examples of such substitutions (e.g., see Ducharme et al., column 7, lines 65-67, "... compounds of formula I, will be useful as a partial or complete substitute for conventional NSAID's in preparations wherein they are presently co-administered with other agents or ingredients"; see also Examples).

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

13. Claims 2, 9 and 19-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Buchmann et al. (WO 94/04522) (Publication Date is **March 3,1994**) (Please note: this reference has the same translation as that of U.S. Patent No. 5,559,134 cited below) (of record) and Futaki et al. (Futaki, N.; Takahashi, s.; Yokoyama, M.; Arai, I.; Higuchi, S.; Otomo, S. "NS-398, a new anti-inflammatory agent, selectively inhibits prostaglandin G/H synthase/cycloxygenase (COX-2) activity in vitro" Prostaglandins **1994**, 47, 55-59).

For ***claims 2 and 9***, Buchmann et al. disclose "new leukotriene-B_4 derivatives ... used in combination ... with cyclooxygenase inhibitors" (see Buchmann et al., page 11, lines 58-65; see also claims 1, 2 and 10), which reads on claim 1. Although the compounds in the Buchmann et al. reference do not explicitly state that the LTB_4 antagonists are "selective" antagonists they share a reasonably close correlation to the structures that are taught in Applicants' disclosure (e.g., they fall within the class of "aryl ethers" as disclosed in Applicants' specification at, page 3, first full paragraph; see also specific examples of "aryl ethers" listed in claims like Lilly LY-293111). "When the

PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For ***claims 19-27***, Buchmann et al. disclose at least 100 mg of a selective leukotriene B_4 receptor antagonist (e.g., see page 11, second full paragraph wherein 200 mg of the leukotriene B_4 antagonist is disclosed).

The prior art teachings of Buchmann et al. differ from the claimed invention as follows:

For ***claims 2 and 9***, Buchmann et al. are deficient in that they do not specifically teach the use of a "selective" Cox-2 inhibitor. Buchmann et al. only teach the use of cyclooxygenase inhibitors, but they do not provide a specific example (e.g., see Buchmann et al., Buchmann et al., page 11, lines 58-65; see also claims 1, 2 and 10).

For ***claims 19-27***, Buchmann et al. fail to disclose at least 35 mg of a COX-2 selective inhibitor.

However, Futaki et al. teach the following limitations that are deficient in Buchmann et al.:

For ***claims 2 and 9***, Futaki et al. (see entire document) teach the use of NS-398, which is a selective Cox-2 inhibitor with an IC_{50} value being 3.8×10^{-6} M versus its Cox-

1 inhibition at 10^{-4} M. Furthermore, Futaki et al. teach (see Futaki et al., abstract; Please note that Cox-2/Cox-1 IC_{50} ratio is "at least 100").

For ***claim 19-27***, Futaki et al. disclose at least 35 mg of a COX-2 selective inhibitor (e.g., see abstract, "1000 mg/kg given orally"). Furthermore, administering the proper dosage of a drug is well within the skilled artisan.

It would have been obvious to one skilled in the art at the time the invention was made to use the Cox-2 inhibitors as taught by Futaki et al. with the LTB_4 antagonists as taught by Buchmann et al. because Buchmann et al. explicitly states that the LTB_4 antagonists can be combined with the Cox-2 inhibitors (e.g., Buchmann et al., Buchmann et al., page 11, lines 58-65; see also claims 1, 2 and 10). A person of skill in the art would have been motivated to use the "selective" Cox-2 inhibitors because Futaki et al. state that NS-398 "produced much smaller gastrointestinal lesions" than other "non-selective" Cox-2 inhibitors like indomethacin which would result in "less gastrointestinal toxicity" (e.g., see abstract; see also page 56, paragraphs 1-2). Furthermore, a person of skill in the art would have reasonably expected to be successful because Futaki et al. state that NS-398 is "almost as potent as indomethacin [i.e., a non-selective Cox-2 inhibitor]" and thus would be expected to act in a similar fashion (e.g., see Futaki et al., abstract).

14. Claims 2, 9 and 19-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Buchmann et al. (US Pat. No. 5,559,134) (Filing Date is **March 23, 1995**; Date of Patent is **September 24, 1996**) (of record) and Futaki et al. (Futaki, N.; Takahashi, s.; Yokoyama, M.; Arai, I.; Higuchi, S.; Otomo, S. "NS-398, a new anti-inflammatory agent, selectively inhibits

prostaglandin G/H synthase/cycloxygenase (COX-2) activity in vitro" Prostaglandins **1994,** 47, 55-59).

For ***claims 2 and 9***, Buchmann et al. disclose "new leukotriene-B_4 derivatives ... used in combination ... with cyclooxygenase inhibitors" (e.g., see Buchmann et al., column 7, lines 58-65; see also claims 1, 2 and 10), which reads on claim 1. Although the compounds in the Buchmann et al. reference do not explicitly state that the LTB_4 antagonists are "selective" antagonists they share a reasonably close correlation to the structures that are taught in Applicants' disclosure (e.g., they fall within the class of "aryl ethers" as disclosed in Applicants' specification at, page 3, first full paragraph; see also specific examples of "aryl ethers" listed in claims like Lilly LY-293111). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For ***claims 19-27***, Buchmann et al. disclose at least 100 mg of a selective leukotriene B_4 receptor antagonist (e.g., see claim 9 wherein 200 mg of the leukotriene B_4 antagonist is disclosed).

The prior art teachings of Buchmann et al. differ from the claimed invention as follows:

For ***claims 2 and 9***, Buchmann et al. are deficient in that they do not specifically teach the use of a "selective" Cox-2 inhibitor. Buchmann et al. only teach the use of cyclooxygenase inhibitors in general, but they do not provide a specific example (e.g., see Buchmann et al., Buchmann et al., page column 7, lines 58-65; see also claims 1, 2 and 10).

For ***claims 19-27***, Buchmann et al. fail to disclose at least 35 mg of a COX-2 selective inhibitor.

However, Futaki et al. teach the following limitations that are deficient in Buchmann et al.:

For ***claims 2 and 9***, Futaki et al. (see entire document) teach the use of NS-398, which is a selective Cox-2 inhibitor with an IC_{50} value being 3.8×10^{-6} M versus its Cox-1 inhibition at 10^{-4} M. Furthermore, Futaki et al. teach (see Futaki et al., abstract; Please note that Cox-2/Cox-1 IC_{50} ratio is "at least 100").

For ***claim 19-27***, Futaki et al. disclose at least 35 mg of a COX-2 selective inhibitor (e.g., see abstract, "1000 mg/kg given orally"). Furthermore, administering the proper dosage of a drug is well within the skilled artisan.

It would have been obvious to one skilled in the art at the time the invention was made to use the Cox-2 inhibitors as taught by Futaki et al. with the LTB_4 antagonists as taught by Buchmann et al. because Buchmann et al. explicitly states that the LTB_4 antagonists can be combined with the Cox-2 inhibitors (e.g., Buchmann et al., Buchmann et al., page column 7, lines 58-65; see also claims 1, 2 and 10). A person of skill in the art would have been motivated to use the "selective" Cox-2 inhibitors because Futaki et

al. state that NS-398 produced much "smaller gastrointestinal lesions" than other "non-selective" Cox-2 inhibitors like indomethacin which would result in "less gastrointestinal toxicity" (e.g., see abstract; see also page 56, paragraphs 1-2), which is of concern for the types of diseases that are being treated by Buchmann et al. (e.g., see column 7, lines 41-49, "... the new leukotriene-B4 derivatives are also suitable ... to treat diseases of the internal organs, in which leukotrienes play an important role, such as, e.g.: allergic diseases of the intestinal tract, such as colitis ulcerosa and colitis granulomatosa"). Finally, a person of skill in the art would have reasonably expected to be successful because Futaki et al. state that NS-398 is "almost as potent as indomethacin [i.e., a non-selective Cox-2 inhibitor]" and thus would be expected to act in a similar fashion (e.g., see Futaki et al., abstract). Furthermore, Futaki et al. explicitly state that NS-398 exhibits "inflammatory and analgesic effects ... with minimum toxicity" and is especially suited for "produc[ing] fewer gastrointestinal lesions" (e.g., see abstract; see also page 57, second to last paragraph), which is exactly what is required to treat the internal chronic inflammatory diseases disclosed by Buchmann et al. including "inflammatory intestinal diseases (colitis); as well as reperfusion damages (to the heart, intestinal or renal tissues" (e.g., see Buchmann et al., column 2, lines 51-61; see also column 7, lines 50-52, "new LTB_4 derivatives ... [are useful in] the treatment of diseases of internal organs with inflammatory processes"; see also column 7, lines 48-49).

Response

15. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed

persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "Buchmann et al. did not describe or suggest combination of an LTB_4 receptor antagonist and a COX-2 inhibitor, and could not have contemplated the combination of an LTB_4 receptor antagonist and a COX-2 selective inhibitor at the time of the filing of their patent" and cite various documents including Masferrer et al. in support of this position (e.g., see 1/27/05 Response, pages 36-37).

[2] Applicants argue, "Buchmann et al. did not provide any motivation to combine an LTB_4 receptor antagonist with a COX-2 inhibitor, let alone a selective COX-2 inhibitor. At the time of filing the application for the '134 patent, one of the most common cyclooxygenase inhibitors was ibuprofen, and one skilled in the art might have interpreted this paragraph as a suggestion to combine the LTB_4 receptor antagonist with ibuprofen or any of the multitude of compounds encompassed by the 11 classes described therein. Such a combination is not a suggestion to combine with a COX-2 inhibitor (e.g., see 1/27/05 Response, pages 38).

[3] Applicants argue, "there was no reasonable expectation of success ... because a subset of compounds encompassed by the 11 classes described therein were not effective in several scenarios of inflammation, in which LTB_4 receptor antagonists showed effectiveness. Specifically, Applicants point to two abstracts, which look at the efficacy of LTB4 antagonists or PAF antagonists administered singly in airway inflammation and sensory neuron inflammation" and cite various references including Richards et al. and Iwamoto et al. in support of this position (e.g., see 1/27/05 Response, pages 38-39).

This is not found persuasive for the following reasons:

[1] In response to applicant's arguments against the Buchmann et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, Applicants' argue that Buchmann et al. does not teach a selective COX-2 inhibitor. However, the rejection is not based on the Buchmann et al. reference alone (i.e., either the WO 94/04522 or US Pat. No. 5,559,134 documents) but, rather, the combination of Buchmann et al. and Futaki et al, which does teach the required selective COX-2 inhibitor (e.g., see Futaki et al., wherein NS-398 is disclosed). The Examiner further notes that "... there is no requirement that the prior art provide the same reason as the applicant to make the claimed invention", see MPEP § 2144"). That is, there is no requirement that Buchmann et al. refer to a cyclooxygenase-2 inhibitor as purported by Applicants.

[2] In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, "A person of skill in the art would have been motivated to use the "selective" Cox-2 inhibitors because Futaki et al. state that NS-398 "produced much smaller gastrointestinal lesions" than other "non-selective" Cox-2 inhibitors like indomethacin which

would result in "less gastrointestinal toxicity" (e.g., see page 55 abstract; see also page 56, paragraphs 1-2). Although Applicants state, "Although Futaki et al. suggests that one selective COX-2 inhibitor caused less gastric lesions than an NSAID, that would not have motivated one skilled in the art to combine NS-398 with other agents" (e.g., see 1/27/05 Response, page 38), this assertion appears to be entirely unfounded as Applicants never provide an explanation or any documentation that would support it.

In addition, the Examiner notes that Buchmann et al. explicitly state that their LTB_4 antagonists can be combined with a cyclooxygenase inhibitor (e.g., see Buchmann et al., column 7, lines 58-65, "new leukotriene-B_4 derivatives ... used in combination ... with cyclooxygenase inhibitors"), which would encompass the cyclooxygenase inhibitor disclosed by Futaki et al. (i.e., NS-397). Furthermore, a person of skill in the art would have been motivated to use NS-398 because it would, for example, result in "less gastrointestinal toxicity" (e.g., see page 55 abstract; see also page 56, paragraphs 1-2), which is of concern for the types of diseases that are being treated by Buchmann et al. (e.g., see column 7, lines 41-49, wherein diseases of the intestinal tract are disclosed). The fact that, Buchmann et al. allegedly do not refer to "selective Cox-2" inhibitors is of no consequence because there is no requirement that the prior art provide the same reason as the applicant to make the claimed invention (e.g., see MPEP § 2144).

[3] The Examiner respectfully disagrees. Applicants cited references have nothing to do with the current rejection. They apply instead to "LTB_4 antagonists + PAF antagonists," not the currently claimed "LTB_4 antagonists + Cox-2 inhibitors." Thus, Applicants' arguments are moot. Applicants argue, "In view of that [i.e., their LTB_4 + PAF analysis], Applicants note that there would have been no reasonable expectation of success in combining other agents suggested

by Buchmann et al., such as LTB_4 antagonists and cyclooxygenase inhibitors [i.e., one bad apple presumably ruins the lot]" (e.g., see page 39, second full paragraph). However, this statement is entirely unsupported. To the contrary, the fact that Applicants could not produce similar abstracts concerning the currently claimed cyclooxygenase inhibitors as stated in the above rejection suggests that no such data exists. Furthermore, Futaki et al. explicitly state that NS-398 exhibits "inflammatory and analgesic effects ... with minimum toxicity" and is especially suited for "produc[ing] fewer gastrointestinal lesions" (e.g., see abstract; see also page 57, second to last paragraph), which is exactly what is required to treat the internal chronic inflammatory diseases disclosed by Buchmann et al. including "inflammatory intestinal diseases (colitis); as well as reperfusion damages (to the heart, intestinal or renal tissues" (e.g., see Buchmann et al., column 2, lines 51-61; see also column 7, lines 50-52, "new LTB_4 derivatives ... [are useful in] the treatment of diseases of internal organs with inflammatory processes"; see also column 7, lines 48-49). Furthermore, obviousness does not require absolute predictability of success; rather, all that is required for obviousness under § 103 is a "reasonable expectation of success." *In re O'Farrell*, 853 F.2d at 903-904 [7 USPQ2d at 1681].

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

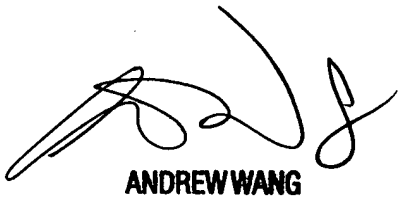
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
September 6, 2005



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